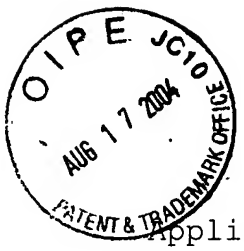
1624



PATENT
1110-0306P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Hidemitsu NISHIDA et al.	Conf.:	9102
Appl. No.:	10/026,606	Group:	1624
Filed:	December 27, 2001	Examiner:	S. Patel
For:	TRICYCLIC COMPOUND HAVING SPIRO UNION		

PETITION UNDER 37 C.F.R. §1.144

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

August 17, 2004

Sir:

Applicants respectfully petition for rejoinder of Groups I and II.

In the Restriction Requirement of November 20, 2003, the Examiner restricted the claims into the following two (2) groups.

Group I, claims 19-29, in part, wherein X is nitrogen; Y is oxygen, NH or imino; m is 0; n is 1, thus forming compounds having 3-fused rings; and

Group II, claims 19-29, in part, drawn to compounds not included in Group 1, wherein X is CH; Y is O, NH, S, SO or SO_2; and m and n form compounds having a 7-membered ring fused with a 6-membered ring or when n is 2 or 3, to form a compound having a 7-

or 8-membered ring, which is fused with a 5-, 6- or 7-membered heterocycle having a Y variable.

The Examiner additionally required an election of species.

On December 22, 2003, Applicants timely elected, with traverse, Group I. In response to the election of species Applicants elected the compound of Example 1.

Applicants, respectfully petition that the restriction of Groups I and II be withdrawn and the subject matter of these groups (claims 19-29 in their entirety) be rejoined.

The different substituents restricted by the Examiner into separate groups are recited as Markush groups. The restriction of elements recited in Markush groups is governed by M.P.E.P. §803.02, which states, "it is improper for the Office to refuse to examine that which applicants regard as their invention unless the subject matter in a claim lacks unity of invention of invention. *In re Harnisch*, 206 USPQ 300 (CCPA 1980)...unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." Both a common utility and a substantial structural feature are present with Groups I and II, so the restriction is entirely without basis.

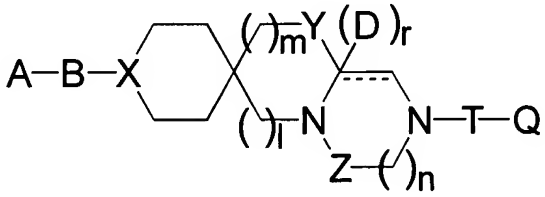
Both the MPEP and case law support Applicants' position that the Examiner's requirement for restriction regarding Groups I and II in this matter is not correct. A short discussion of Harnisch is useful given the MPEP's reliance on this case. Claim 1 of Harnisch was directed to courmarin compounds. The Examiner in Harnisch rejected the claims under 35 U.S.C. §121 "as containing an improper Markush group and misjoinder." The Examiner in the present application is using virtually the same reasoning as in Harnisch in support of the restriction requirement, that is, "the instant generic claim constitutes an improper joinder of inventions." See, for example, Paragraphs 5 and 6 on pages 4 and 5, of the Office Action. The common utility and shared substantial structural feature, which is essential to the utility of the invention are discussed below.

(1) Common utility -

The present invention is based on the discovery by the inventors that compounds of Formula (I) with a tricyclic core with a spiro union have the common utility of inhibiting activated blood coagulation factor X (FXa) and therefore acting as anticoagulants. See page 1, second paragraph of the specification.

(2) Shared substantial structural feature disclosed as being essential to the common utility -

The compounds of Groups I and II share the common structural feature of a tricyclic compounds having a spiro skeleton. See Formula (I) below.



(I)

The present invention is based on the discovery that the compounds of formula (I) having the indicated spiro skeleton have extremely potent FXa inhibitory activity, as described on page 11 lines 3 to 9 of the specification. The compounds of the invention have a novel tricyclic structure having a spiro union, e.g., 1,4-diaza-7-oxa-1'-spiro[bicyclo [4.3.0] nonane-8, 4'-piperidin] ring, 1,4,7-triaza-spiro [bicyclo [4.3.0] nonane-8, 4' -piperidin] ring or the like.

The novel structure of the invention is very important. As discussed in the Examples describing the X-ray crystallography analysis, found on line 15 of page 350 through line 9 of page 358 in the specification and from line 23 of page 357 to line 9 of page 358, the tricyclic compounds of the invention, including the novel

spiro union, contributed to having been able to find the novel pharmacophore of the invention, which had not been reported for already-known Fxa inhibiting compounds, by fixing the tricyclic three-dimensional conformation to specific coordinate positions.

As discussed on page 9, lines 1-17 of the specification, the present invention determined, for the first time, what kind of structure should be studied for developing different types of FXa inhibitors. In addition, as a result of the present work, the demerits of already-known FXa inhibitors such as DX-9065a and FX-2212a, whose availability with oral administration is insufficient and which have side effects from amidino groups or guanidine groups, were overcome. The information obtained from the present work regarding the interactions between FXa and FXa-inhibitory compounds based on the data of the crystal structure of the complex between the FXa and the FXa-inhibitory compounds of the invention is ground-breaking and extremely important in the field of FXa inhibitors.

The Examiner asserts that the substituents in the generic formula (I) of Group I (e.g. X, Y, m, l and n) should be limited as discussed on page 2, Item 3 of the Restriction Requirement of November 20, 2003, a copy of which is attached hereto. Specifically, the Examiner asserts that the working examples only

disclose 6:5:6 rings and that other combinations, such as 6:6:6, 6:7:6 or 6:7:7 tricyclic heterocycles are not supported by the specification.

However, the Examiner is mistaken in this position. Attention is directed to Example 8 of the specification, which discloses a tricyclic heterocycle that is a 6:6:6 combination and has the spiro frame structure of 2,4-diaza-7-oxa-spirobicyclo [4.4.0]decane-2-one. Thus, the specification discloses other than 6:5:6 combinations. This compound is described on page 207, line 17 to page 212, line 16, including the detailed description of the synthesis of the compound. As discussed in the specification, the compound of Example 8 can be synthesized using the general production methods of the invention that are described on page 93, line 23 to page 144, line 6 of the specification. Other ring combinations are similarly sufficiently disclosed from the general production methods, which include various ring combinations. As such, Applicants believe that the invention should not be limited as suggested by the Examiner.

In addition, the Applicants have tested several additional compounds having various sizes of spiro rings and heteroatoms that are encompassed by formula (I). The structures of the Compounds (1) to (7) are shown on "Attachment A". The Compounds (1) to (7)

were synthesized using the methods described in the specification. The compounds (1) to (7) are also shown in the Table 1, below, wherein it is shown that the compounds have an inhibitory activity within the range recited in the specification on page 165, lines 3-6.

TABLE 1

Compound	Ring Combination	Y	M	l	n	IC50(nm)*
1	6:5:6	S	0	1	1	1.3
2	6:5:6	SO_2	0	1	1	2.3
3	6:6:6	NH	1	1	1	3.5
4	6:6:6	S	1	1	1	25
5	6:5:7	NH	0	1	2	11
6	6:6:7	NH	1	1	2	884
7	6:5:7	O	1	0	2	96

*Fxa inhibitory action was measured in accordance with the test method described on page 164 of the specification.

As noted above, not only 6:5:6 ring combinations, but various other ring combinations can also be produced using the methods described in the specification. In addition, compounds may be made wherein Y is S or SO_2, or wherein m is 0 or 1; l is 0 or 1; and n is 1 or 2. The Fxa inhibitory action with the above-compounds is within the range of the inhibitory action described in the specification on page 165, lines 3-6.

The data of Table 1 evidences that compounds exemplifying the full scope of Formula (I) can be synthesized using the methods described in the specification and such compounds have inhibitory

activity for Fxa as described in the specification. Accordingly, Applicants assert that specification as originally filed contains sufficient support for the scope of the claimed invention and it is not necessary to further limit the definitions recited for formula (I).

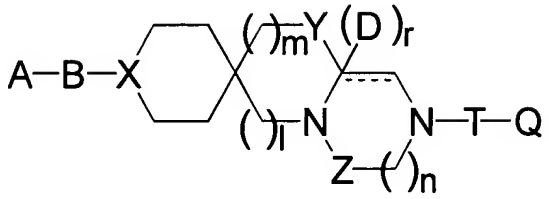
Finally, Applicants note that the Examiner indicates in the Office Action of March 17, 2004, that a search of the compounds in Group I results in more than 4000 total hits. However, if the invention is structure searched using the CAS:STN Registry, which is commonly used to in the field of chemistry, there are only 599 compounds/hits total. In addition, all of the compounds are embodied in either WO/02/05368 (corresponding to U.S. App. No. 10/451,728) or the present application, which has the same assignee as the '728 application.

The REGISTRY File is a chemical structure and dictionary database containing substance records for substances identified by the CAS (Chemical Abstracts Service) Registry System. The database includes substances indexed in Caplus, CA and CAOLD files, as well as special registrations for, for example, regulatory lists such as TSCA and EINECS.

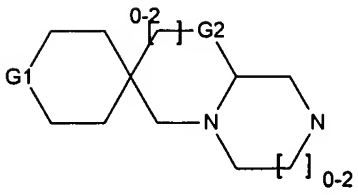
When the present invention is search using the following partial structure search with the REGISTRY File, as indicated above

only 599 compounds are identified, which fall in only two references.

Formula (I)



(I) m=0,1,2 n=0,1,2 l=1
X=C,N Y=N,O,S



G1=C,N
G2=O,S,N,C

Applicants note that "l" was fixed as 1 for search. Using this standard search strategy, it is possible to search the skeletons having ring sizes of 6-5-5, 6-5-6, 6-5-7, 6-6-5, 6-6-6, 6-6-7, 6-7-5, 6-7-6, 6-7-7 as one search with one search formula. It is easily recognizable from this search that the compounds of formula (I) have unique spiro skeleton.

Thus, the compounds of Groups I and II share a common structural feature of the tricyclic core having a spiro union and this spiro skeleton has been shown to be essential for the common utility of FXa inhibitory activity. As such, Applicants respectfully petition for rejoinder of the claims of Groups I and II.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong (Reg. No. 40,069) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr., #28,977

MaryAnne Armstrong, Ph.D., #40,069

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1110-0306P
GMM/MAA/

Attachments: Restriction Requirement of November 20, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,606	12/27/2001	Hidemitsu Nishida	1110-0306P	9102

2292 7590 11/20/2003

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12.20.03 mm
DOCKETED ES
Restriction
Seq. Listing

EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,606	NISHIDA ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *19-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *10*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' communication paper # 9 dated 10/14/03 is acknowledged. Applicants have **cancelled old claims 1-18** and presented **new claims 19-29** while confirming that the subject matter of cancelled claims 6-9, 13 has been deleted from the above stated new claims. Applicants have presented their counter proposal for the restriction/election. Applicants have not confirmed the election of a group from the newly proposed groups, and have not also elected the species as required by the earlier Office communication paper # 8 dated 9/12/03.

2. The examiner regrets the typo error of reciting –CH- as –CH2-. Applicants' arguments and remarks have been considered favorably, and found persuasive for the regrouping of the inventions.

3. **Examiners' position regarding restriction/election:** Upon reviewing this application further, examiner found that the working examples as recited in specification pages 177-301 and in Table of pages 302-315, mostly consist of Y = Oxygen or NH or NMe; X = N; m = zero; l = one; n = 1 i.e. tricyclic combination of ***6:5;6 rings*** which are actually made and tested. It is believed that there is no support for the other combinations as claimed herein e.g. Tricyclic heterocycles having**: 6:6:6 or 6:7:6 or 6:7:7 combinations**. Therefore, Examiner initiated the discussion with applicants (see interview summary dated 11/18/03, attached with this paper). Applicants desired a written document for discussion with their overseas clients to reply this action. Based on above data the restriction/election has been compacted as follows.

Election/Restrictions

4. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims (in part) 19-29, drawn to tricyclic-spiro compounds of generic formula (I), wherein X is Nitrogen, Y = oxygen atom, NH or imino group optionally substituted, integer m = zero, integer l = 1, integer n = 1 i.e.3-fused rings combination as 6-membered saturated piperidine-50membered saturated hetero-ring with Y – O or imino-6-membered 1,4-diaza-piperazine consisting of; (1). Piperidine-1,4diaza-7-oxa-spirobicyclo[4,3.0]-nonanone or (2). Piperidine- 1,4,7-triaza-spirobicyclo [4.3.0] nonan-2-one, classified in **class 544**, subclasses 358,380,384; utility **class 514**, subclasses 248,245,250,252.15,252.13.

II. Claims(in part)19-29, and subject matter of old non-elected/cancelled claims 6-9,13 drawn to compopunds/intermediates not included in invention of Group I, their composition and a method of use(where applicable). e.g. compounds for Formula (I) wherein X = -CH- i.e. forming 6-membered Benzene; Y = -NH-, O, S, SO or SO2; integers m, n forming a ring with 7 members wherein1, 3-diaza- or 1,3 oxazo- or 1,3-thiaza-7-membered ring is fused with 6-membered ring 1 N or alternatively, when integer n = 2 or 3, forming a 7- or 8-membered 1,4-diaza-heterocycle which is fused with 5- or 6- or 7-membered heterocycles having Y variable, classified in various classes. e.g. a few of which are, compound **class 540**, **utility class 514**, subclasses various depending on the nature

of the variables. If this group is elected, further restriction/election will be required as there are many unknowns. Additionally, a single species (from the actual working example (with all variables exactly and definitely known) must be disclosed.

5. The inventions are distinct, each from the other because of the following reasons:

The groups as presented above, are distinct inventions, each from the other because of the following reasons: The compounds of Groups I-II are drawn to:

(1). Structurally diverse compounds that are made and used independently of each other;
(2). Compounds are separately classified;
(3) Classes will require separate literature searches;
(4) Compounds are not art recognized equivalents, and additionally,
(5). The groups lack unity of invention(see MPEP 803.02).

Based on above stated data i.e. (1) - (5), it is believed that claim 1 also lacks unity of invention. The chemical structures are different with multiple values of the variables. e.g. when variable A is Hydrogen atom the compound is unsubstituted B or X variable; when A is a saturated 5- or 6- membered cyclic hydrocarbon group it is cyclopentane or cyclohexane, and when A is a saturated or unsaturated 5- or 6-membered heterocyclic group there are many more unknown possibilities. Note, claim 1 remains silent about the exact nature, size of the ring, and make up of the heteroatoms(s) in a heterocycle together with the exact point of attachement with carbon atom of the main core/bridge.

6. Inventions I-II are related as product, its composition, and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different

process of using that product (MPEP § 806.05(h)). In the instant case Compounds of WO 9616940 as well as Das et al(U.S.P. 5691356) can be also used for the utility as claimed herein.

7. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

8. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

9. Claims 19,22,23, 24,25,26,27-28 are generic to a plurality of disclosed patentably distinct species comprising (where applicable) **(1).** A variable having meanings H, Hydrocarbon, 5 or 6-membered heterocycle, -NH2, imidoyl; **(2).** B = absent or forming a CO or S, So SO2 or alkylene; **(3).** X is N or CH2 i.e. forming cyclohexane or piperidine cores; **(4).** Integers m + l = 1 i.e. forming a 5-membered ring with Y (= O/S/SO/SO2/NH) and N; **(5).** Integers m + l =2 i.e. forming a 6-membered ring; **(6).** Integers m + n = 3 i.e. forming a 7-membered ring; **(7).** Integers m + n = 4 i.e. forming an 8-membered ring respectively. Additionally, the components T & Q, and values of integer n =0-2 will provide further many compounds, which are not chemical equivalents of each other.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species from the working example, even though this requirement is traversed.

10. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

11. A telephone call was made to Dr. Ms.Armstrong on 11/17/03 to request an oral election to the above restriction requirement, but did not result in an election being made as applicants desired a written document for discussion(s) with their clients abroad.(See enclosed interview summary).

12. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

13. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Additional formalities to be completed by applicants:

14.1. This application as received by the examiner did not contain a computer readable disc for the Sequence listing to be approved by the people concerned. Therefore, the

same has not been recorded by the Office. Applicants are urged to act accordingly to avoid unnecessary delays at a latter stage prior to allowance of this application.

14.2. It is believed that applicants have not recited/provided the correct PCT International Application NO._____ as well as its English version/translation. It will be necessary for the examination because the ***instant application is a continuation in part of the said International Application NO***._____, with a filing date_____, published on _____. Applicants are urged to provide the same to the office for a proper, thorough, and complete examination by the examiner.

14.3. Additionally, the U.S. Application Sr. NO. 1045728, filed on 6/25/03, which is a national stage application and is a 371 of PCT/JP01/11656, filed 12/28/2001 will raise other issues. e.g. double patenting. See copy of the claims enclosed with this communication.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm.Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr.Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at 703 308 4523.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

Sudhaker B. Patel, D.Sc.Tech.
November 18, 2003.

MUKUND SHAH
SUPERVISORY PATENT
EXAMINER
ART UNIT 1624